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Customer No.: 07278
PATENT TRADEMARK OFFICE

Docket No: 0632/0D916

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Hsien-Jue CHU

Serial No.: 09/007,385 Art Unit: 1647

Confirmation No.:

Filed: January 15, 1998 Examiner: S. Turner

For: STREPTOCOCCUS EQUI COMPOSITIONS AND METHODS OF USE

DECLARATION UNDER 37 C.F.R. §1.132 OF WUMIN LI

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

March 13, 2002

Sir:

I, Wumin Li, declare and state that:

1. I was awarded a D.V.M. in 1982 from the School of Veterinary Medicine, University of Shenyang, China. I was awarded a Ph.D. in 1993 from the University of Wisconsin-Madison, Department of Animal Health and Biomedical Science. From 1995 to the present I been employed at Fort Dodge Animal Health,

Brudall 6-6-02

Division of Wyeth, Fort Dodge, Iowa, as a project leader/manager in Biological Research & Development. My responsibilities include managing and conducting research and development in the area of bacterial vaccines for large animals, including bovine, equine and swine. I have extensive experience in the field of research and development of animal vaccines. I have particular expertise in the field of bacterial vaccines for bovine, equine and swine. I am also familiar with the extensive literature in animal vaccinology. My qualifications are explained in greater detail in the attached copy of my Curriculum Vitae (Exhibit A).

2. I am not a co-inventor in the above-identified application.

3. I have read the above-captioned application and am familiar with its contents, including the claims. I have also reviewed the Office Action dated December 13, 2001, and the references cited against the claims, Timoney (U.S. Patent No. 5,183,659) in view of Hartford (EPO 786518A1), Estrada (U.S. Patent No. 5,597,807), and additionally Timoney and Galan (Recent Advances in Streptococci and Streptococcal Diseases, Reedbooks Ltd., 1985: Proceedings of the IXth Lancefield International Symposium on Streptococci and Streptococcal Diseases held in September 1984, pp. 294-5). It is my understanding that the claims have been rejected as follows:

I. The claims are rejected because it allegedly would have been obvious to combine an avirulent strain of Streptococcus equi (S. equi) with saponin to obtain an S. equi vaccine which induces an immune response.

II. The claims are rejected because it allegedly would have been obvious that an S. equi vaccine would induce protective immunity in horses based on the results in a mouse model that showed that an S. equi vaccine stimulated an immunological response in mice.

III. The claims are rejected because it allegedly would have been obvious that a protective immune response would be obtained upon administration of an S. equi vaccine if antibodies are produced in response to administration of the vaccine.

4. Drawing on my knowledge of animal vaccinology, it is my opinion that:

I. It would not have been obvious to combine an avirulent strain of S. equi with saponin to obtain an S. equi vaccine which induces a protective immune response.

A) At the time of the invention, the efficacy of saponin as an adjuvant was not predictable. Based on knowledge at the time of the invention, one of skill in the art would not have been able to predict that saponin would be consistently potent. At the time of the invention, one of skill in the art would not have been able to predict that saponin would be equally effective as an adjuvant across species.

For example, in the case of foot and mouth disease (FMD), it was shown that saponin greatly enhanced the immunogenicity of FMD vaccines in cattle and sheep, but not in swine. However, DEAE-dextran and oil had more efficacy as adjuvants in pig vaccines. See F. Sôlyom, International Symposium on pyrogenicity, innocuity and toxicity test systems for biological products, Budapest 1976, Develop. Biol. Standard, 34: 169-178 (S. Karger, Basel, 1977) (Exhibit B). Thus, it would not have been predictable that saponin would enhance the immunogenicity of a vaccine in all species if it was shown to do so in one species.

In addition, typical saponin preparations are widely known to have adverse biological effects, e.g., saponin has been reported to cause severe tissue injury or inflammation. See id. at 169. Therefore, one of skill would not have been able to predict that saponin would not have biological side effects (toxicity) to the vaccinated subject. One of skill also would not have been able to predict that saponin would not have an adverse effect on the infectivity and immunogenicity of antigens.

B) At the time of the invention one of skill in the art would not have been able to predict that saponin would be equally effective as an adjuvant with any antigen. The adjuvant activity of saponin is dependent upon the particular antigen used and the immunogenicity of the antigen. See R. Bomford, Int. Archs Allergy appl. Immun., 1984, 75: 280-281 (Exhibit C). Thus, without testing the particular combination of a target antigen and saponin, one would not have been able to predict that saponin would be an effective adjuvant or that it would not have a detrimental effect on the immunogenicity of the antigen.

C) At the time of the invention, one of skill in the art would have known that not all adjuvants have the same efficacy. For example, a comparative study of the adjuvants saponin and DEAE-dextran used with foot-and-mouth disease as the antigen, showed that saponin was less potent than the DEAE-dextran. See Anderson EC et al., Res. Vet. Sci.,1971, 12:351-357 (Exhibit D). Anderson also disclosed that the two adjuvants produced different levels of antibody responses in animals compared to emulsion vaccines. The DEAE-dextran stimulated reasonable serum neutralizing antibodies after a single administration and lasted for 1-3 months. In contrast, a single dose of saponin resulted in a primary response that lasted 21 days, at which time no serum antibody was detectable.

In view of these results, one of skill would not have been able to predict that an antigen adjuvanted with saponin would provide an adequate immune response upon a single innoculation.

Based on the foregoing, it is clear that one of skill in the art at the time of the invention would not have been able to predict that saponin would induce an immune response or enhance the immunogenicity of an antigen. Therefore, it would not have been obvious to combine an avirulent strain of S. equi with saponin to obtain an S. equi vaccine which induces an immune response.

II. It would not have been obvious that an S. equi vaccine would have induced protective immunity in horses based on the results in a mouse model that showed that an S. equi vaccine stimulated an immunological response in mice.

Although the mouse may have "historically" been used as a model to investigate disease in horses, one of skill in the art would not have been able to predict or extrapolate immunological effects in horses from the mouse model. This knowledge was not only true at the time of the invention, but was known as late as 1999.

For example, in a study of equine herpesvirus-1 (EHV-1) infection, the authors noted that many problems are inherent in the selection of appropriate small laboratory animals as models for large animals, such as horses. See Walker C et al., Vet. Microbiol., 1999, 68:3-13 (Exhibit E). These problems included differences in modes of infection or transmission, the types of disease produced, the symptoms of the disease, the tissues affected, and the cycle of the disease in the host. After examining parameters such as tissue tropism, clinical signs of infection, effects of the virus on pregnancy, hematological changes, viral clearance, histopathology, and latency, the authors conceded that the mouse model was a valid model to study the disease itself.

However, the authors concluded that extrapolations of immunological parameters from the mouse to the horse could not be determined due to the failure to provide relevance to that disease under investigation in the target species. See id. at 10.

Thus, based on the state of the art at the time of the invention, as evidenced by the state of the art even as of 1999, immunological parameters could not have been extrapolated to the horse from the effects of the vaccine observed in the mouse model. Therefore, it would not have been obvious that an S. equi vaccine would induce protective immunity in horses based on the results in a mouse model that showed that an S. equi vaccine stimulated an immunological response in mice.

III. It would not have been obvious that a protective immune response would be obtained upon administration of an S. equi vaccine if antibodies are produced in response to administration of the S. equi vaccine.

It is well known to those of skill in the art that even though antibodies are produced in response to administration of a vaccine, the vaccine would not necessarily produce a protective effect.

For example, it has been shown in a study of feline immunodeficiency virus (FIV) that although antibodies were detected in the serum of all animals vaccinated, all animals proved to be infected after challenge. See Huisman W et al., Vaccine, 1998, 15:181-87 (Exhibit F). In some cases, the vaccinated animals even exhibited accelerated viraemia. See id. at 186.

Thus, based on the state of the art at the time of the invention, and even as of 1998, one of skill in the art would not have been able to predict from the level of antibody detected in an animal's serum after vaccination whether the vaccine provided a protective immune response.

Therefore, it would not have been obvious that a protective immune response would be obtained upon administration of an S. equi vaccine if the prior art showed that antibodies are produced in response to administration of an S. equi vaccine.

I declare further that statements made in this Declaration are of my own knowledge and are true and that all statements made on information and belief are believed to be true and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 3-13-2002 Signature: Wenyi Li

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